REMARKS

Upon entry of the amendments herein, claims 1-9 and 12-25 remain pending in the application. Claims 1-5 and 12-18 have been amended; and claims 26-28 have been cancelled. No new matter has been introduced by the amendments herein.

The Examiner has maintained the objection to the pending claims because generic formula I contains "compounds drawn to the non-elected inventions to the extent that it reads on compounds other than R_1 = pyridyl." Claims 1-5 have been amended herein to limit substituent R_1 to pyridyl substituted with one or more basic groups.

The Examiner has requested that the application title be amended to put it in line with the scope of elected subject matter. Applicants have amended the title essentially as suggested by the Examiner.

Claims 12, 13, 16 and 17 remain rejected under 35 USC §112, first paragraph on the ground that the specification does not provide enablement for prevention of the recited disorders. In the first place, the Examiner asserts that "the state of the art is that no general procedure is art-recognized for determining which patients generally will become diseased before the fact" and, further, that "[T]here is no evidence of record that would

guide the skilled clinician to identify those who have the potential of becoming afflicted." The Examiner further asserts that prevention of diseases that are the subject of the present application, e.g., those linked to thrombosis and hypercoagulability, "would require extensive and potentially open ended clinical research on healthy subjects." [Emphasis added.] Applicants do not agree with any of these facets of the Examiner's assessment.

The Examiner believes that one of skill in the relevant art would be "a Board Certified physician in cardiology with an MD degree and several years of experience." Such an artisan would have access to the Sixth (2000) ACCP Guidelines for Antithrombotic Therapy for Prevention and Treatment of Thrombosis (Hirsh, et al., CHEST 2001; 119:1S-2S, copy provided herewith) and, in fact, access to all of the studies reported at the Sixth ACCP Conference on Antithrombotic Therapy. These Guidelines are designed to assist clinicians in their work to prevent or effectively treat thrombotic disorders in their patients. The Guidelines state that the knowledge of specific risk factors in patient groups or in individual patients forms the basis for the appropriate use of prophylaxis of thrombosis. Thromboprophylaxis is currently recommended for several patient groups.

The Examiner is referred to a report, "Prevention of Venous Thromboembolism," (Geerts, et al., CHEST 2001; 119:132S-175S, copy provided herewith) from the Sixth ACCP Conference. For venous thromboembolism (VTE), clinical risk factors include the following: increasing age, prolonged immobility, stroke, or paralysis; previous VTE; cancer and its treatment; major surgery (particularly operations involving the abdomen, pelvis, and lower extremities); trauma (especially fractures of the pelvis, hip or leg); obesity; varicose veins; cardiac dysfunction; indwelling central venous catheters; inflammatory bowel disease; nephrotic syndrome; and pregnancy or estrogen use. These risk factors are present, often in combination, in a high proportion of hospitalized patients. Clearly, by consulting the Geerts report and the Guidelines the skilled artisan would be able to identify patients in need of thromboprophylaxis.

Furthermore, in "Antithrombotic Therapy in Atrial Fibrillation" (Albers, et al., CHEST 2001; 119:194S-206S, copy provided herewith), also reported at the Sixth ACCP Conference on Antithrombotic Therapy, it is reported that atrial fibrillation (AF) is an important independent risk factor for stroke. High-risk factors include prior stroke/transient ischemic attack, or systemic embolus, history of hypertension, poor left ventricular systolic function, age greater than 75

years, rheumatic mitral valve disease, and prosthetic heart-valve. Again, then, consultation of the Albers report in combination with the Guidelines would enable the skilled artisan to identify patients in need of thromboprophylaxis.

Moreover, "Antithrombotic Agents in Coronary Artery Disease" (Cairns, et al., CHEST 2001; 119:228S-252S, copy provided herewith), also reported at the Sixth ACCP Conference, discloses that patients with acute myocardial infarction, unstable angina and chronic coronary artery disease have an increased risk of thromboembolic disease. Combining the Guidelines with the Cairns report would enable one of skill in the art to identify patients in need of thromboprophylaxis.

Similarly, "Antithrombotic and Thrombolytic Therapy for Ischemic Stroke" (Albers, et al., CHEST 2001; 119:300S-320S, copy provided herewith), also reported at the Sixth ACCP Conference, discloses that patients with symptomatic carotid stenosis, prior stroke/transient ischemic attack, transient monocular blindness and asymptomatic carotid disease have an increased risk of suffering ischemic stroke. Referring again to the Guidelines together with the second Albers report, one of skill in the art would be able to identify patients in need of thromboprophylaxis.

Still further support for the idea that thromboprophylaxis is possible and useful is provided by the report of Cohen in Seminars in Thrombosis and Hemostasis 28, suppl. 3, 13-17 (2002). A copy of this article is also provided herewith.

Thus, it is possible to identify patient groups or individual patients who may acquire diseases associated with, e.g., thrombosis or hypercoagulability, before they exhibit (or re-exhibit) symptoms. To answer the Examiner's question, in light of all the knowledge accumulated in the field Applicants and anyone of skill in the art do have a "method of predicting."

In making this rejection, the Examiner refers a number of times to cardiovascular disease and seems to regard the present situation as one in which Applicants are claiming a method for preventing "cardiovascular diseases generally." While it is reasonable to draw a connection between hypercoagulability or thrombosis and diseases that could arise from such conditions and while Applicants have made this connection in the specification, the fact is that the claims are directed literally to prevention of diseases for which inhibition of CPU would be required or desired. In fact, the claims have been amended to make this clearer; this is discussed in greater detail later herein in Applicants' response to the Examiner's rejection of the claims as being nonenabled for the scope of

diseases to be treated. As also discussed and supported later in this response, there certainly has been established a correlation between CPU inhibition and prevention and treatment of disease.

The Examiner asserts that "[T]he only established prophylactics are vaccines not the pyridine mercapto carboxylic acid compounds such as present here." The real question, however, is whether or not one of skill in the art would find credible the assertion that the instant compounds can be effective in the prevention and treatment of diseases in which inhibition of CPU is required or desired. Applicants have provided a strong showing of the potency of the instant compounds as CPU inhibitors and have provided ample showing that patients who would benefit from prophylaxis can easily be identified and targeted.

The Examiner goes on to assert that no evidence has been supplied that "there is any correlation between the inhibition of CPU and the prevention of any disease." The Examiner cites as support for this assertion the last line of the abstract of the Boffa reference which, in the Examiner's words, "clarifies the speculative nature of clinical uses of such inhibitors." Applicants note that the last line (sentence) reads: "This review provides a general overview of the TAFI pathway,

including a discussion of the spectrum of inhibitors of TAFI that have been described, and summarizes the recite advances in the molecular genetics of the TAFI gene as well as the results of studies that may implicate the TAFI pathway in risk for arterial and venous thrombotic disorders." It is not seen how this disclosure supports the Examiner's contention of a lack of correlation between CPU inhibition and disease prevention.

Still further, the Examiner asserts that "data on only forty species is hardly commensurate with the scope of the claims." Applicants wish to remind the Examiner that, forty examples is a relatively large number in the context of applications for patent and satisfaction of the requirements for support of a claimed invention. The Examiner is invited to consider the multitude of issued patents claiming large genera of compounds and supported by far fewer examples. The Examiner's statement as to the requirement for number of examples is arbitrary and inappropriate.

Claims 12, 13, 16 and 17 also remain rejected under 35 USC §112, first paragraph on the grounds that treatment of "conditions associated with inhibition of carboxypeptidise U" is not enabled by the specification. The Examiner again refers to the Boffa reference and the last line of the abstract, which is said to clarify the speculative nature of clinical uses of such

inhibitors as those in the instant invention. Again, it is not seen how the Boffa citation, quoted above, provides support for the Examiner's contention. In any event, regardless of what the Examiner may be referring to, there is ample knowledge in the field to make a connection between CPU inhibition and disease treatment.

In leveling this rejection, the Examiner states: "The issue concerns the correlation between the bio-assays discussed below and clinical efficacy for disease treatment." Applicants respond as follows:

In the last few years, extensive work has been done to try to understand the relationship between proCPU/CPU and disease in humans. In parallel, the scientific society has built up knowledge by using different *in vitro* (blood/plasma from man as well as from different animal species) and *in vivo* models. There are today several published animal studies demonstrating that inhibition of CPU results in an anti-thrombotic effect by stimulation of endogenous fibrinolysis. Inhibition of CPU does not affect coagulation, and in animal models it has been proven to be a very safe principle. The anti-thrombotic animal models used comprise both venous and arterial models as well as models with micro-thrombi. The models are designed to reflect different states in human thrombotic diseases. Thus, inhibition

of CPU is most likely an effective way to treat thromboembolic disorders in humans. In any event, the known studies provide ample credibility for the assertion that such is the case.

Applicants provide herewith copies of a number of more recent studies clearly showing not only that much of relevance to the issue raised by the Examiner was already known at the time the Boffa review was published, but that this area of investigation has progressed greatly since then. The references are listed below, with a brief explanation of the relevance of each to the present assessment of patentability. Again, copies of all of these references are provided herewith.

1) Barrow et al., J. Med. Chem. 46, 5294-5297 (2003). This paper describes the effect of a CPU inhibitor in a thrombosis model in African green monkeys. This animal model has been validated with clinical agents like antiplatelet agents (aspirin, GpIIb/IIIa inhibitors) and direct and indirect thrombin inhibitors.

2) Muto et al., Eur. J. Pharmacol. 461, 181-189 (2003). This paper describes the effect of a CPU inhibitor in a microthrombosis model in the rat. This is a model of the micro-thrombi-related thromboses occurring in various diseases such as bacterial infection, inflammation, thrombotic microangiopathy and disseminated intravascular coagulation.

3) Suzuki et al., J. Pharmacol. Exper. Ther. 309, 607-615 (2004). This paper describes the effect of CPU inhibition in a microthrombosis model in the rat, as well as in an arteriovenous shunt model in the rat.

4) Hashimoto et al., Thromb. Haemost. 87, 110-113 (2002). This paper describes the effect of a CPU inhibitor in an arterial thrombolysis model in the rat. This animal model has been validated with thrombin inhibitors.

5) Wu et al., Thromb. Haemost. 90, 414-421 (2003). This paper describes the effect of CPU activity in a rat model of intravascular fibrin deposition.

6) Nagashima et al., Thromb. Res. 98, 333-342 (2000). This paper describes the effect of a CPU inhibitor in combination with tPA in a rabbit jugular vein thrombosis model.

7) Redlitz et al. Circulation 93, 1328-1330 (1996). This paper describes the correlation between CPU activity and time to restoration of blood flow in a dog model of coronary artery thrombosis. This is a model of the thrombosis occurring in diseases such as myocardial infarction.

Thus, it is clear that much work has been done in the field demonstrating the allegedly missing connection between CPU

inhibition and treatment of the disease recited in the instant claims.

The Examiner asserts as a basis for the rejection that "no carboxypeptidase U inhibitor has ever been used to treat any human disease...." [Emphasis added.] Clearly, this should not be a basis for rejection. As the Examiner must be aware, it is rare that new compounds presented for patent have already been tested in humans. The criteria for establishing credible utility have always been demonstration of asserted properties in a valid *in vitro* system or, at the very most, demonstration *in vivo* in an accepted animal model. Applicants have satisfied both prongs by providing data on the potency of compounds as CPU inhibitors and by providing multiple examples of animal studies linking CPU inhibition with alleviation of disease conditions and/or conditions leading to disease.

The Examiner again attempts to minimize Applicants' showing of data on numerous compounds demonstrating their effectiveness as CPU inhibitors. The Examiner notes that not all of the examples are in the subgenus of pyridine compounds presently being examined; the Examiner is reminded that this is because of the restriction requirement that he himself imposed. Furthermore, the fact that some of the compounds that were tested and found effective do not fall in the present subgenus

under examination is proof that, the diversity of compounds notwithstanding, said compounds are joined by the nexus of effectiveness as CPU inhibitors. The Examiner cannot have it both ways.

The Examiner also takes exception to the fact that there is a 1,000-fold difference in potency between the compounds of Examples 6 and 8. The Examiner in effect penalizes Applicants for providing the comprehensive data that they have. Regardless of differences in potency among the tested compounds, the fact is that all (40) of them have been shown to have significant potency as CPU inhibitors; one of skill in the art would appreciate that even Example 8 is potent enough as a CPU inhibitor to be considered as a possibility in treatment of diseases wherein CPU inhibition is required or desired.

Further along these lines, the Examiner notes the relatively small structural difference between Examples 6 and 8 and uses this as a basis for questioning the effectiveness of "the broadly diverse thousands of compounds of formula I." The Examiner is again reminded of his own restriction requirement; in this case, the result of such is that the diversity to which the Examiner refers is not even relevant to the subject matter currently under examination. With respect to the difference structurally between Examples 6 and 8, the Examiner is again

reminded of the weight of evidence in support of the contention that Applicants are entitled to the claimed subgenus of compounds. The Examiner is further reminded that the standard is not the comparison of compounds within the genus of those being claimed but the comparison of those claimed with what was previously known. The demonstration of potency of 40 instant compounds is more than enough to provide credibility to the assertion of effectiveness of the genus in general and to show that said genus represents a patentable improvement over what was previously known. The Examiner's response to the difference in potencies among the tested compounds, the apparent expectation that each and every compound be tested, is certainly unreasonable.

Claims 12, 13, 16 and 17 stand newly rejected under 35 USC 112, second paragraph as indefinite for recitation of "conditions associated with inhibition of carboxypeptidase U."

The claims have been amended to more clearly recite the nexus that unites the diseases that would be expected to be treatable by use of the CPU inhibitors according to the instant invention. Applicants note that the Examiner, in asserting that the scope of diseases to be treated is too broad, states that the instant claims read on "conditions which cause inhibition of CPU...." It must be emphasized that the intention of the

claimed invention is treatment of conditions that respond favorably to inhibition of CPU, not treatment of conditions which cause inhibition of CPU. Thus, in the interest of clarity as well, Applicants have amended the claims to address both the nonenablement and indefiniteness issues with respect to the diseases to be treated. It should be noted that the amendments include replacement of the "associated" language that was of concern to the Examiner. One can readily determine the types of diseases that may be amenable to treatment with the instant compounds and which patients may benefit most from such treatment; in other words, the metes and bounds of the claimed invention are readily determined.

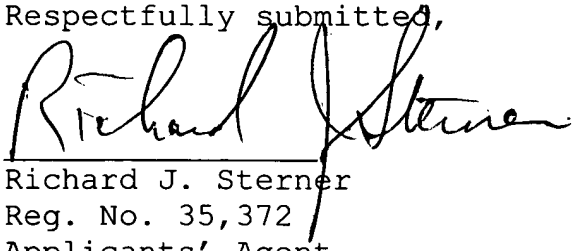
Claims 1-9, 14, 15 and 18-28 were merely objected to because their scope was not in conformance with Applicants' election of subject matter; the claims have been amended to address this issue. As supported by Applicants' arguments and the additional showing provided herewith, claims 12, 13, 16 and 17 are both enabled and definite with respect to the scope of recited diseases and enabled for prevention of said diseases. Accordingly, all pending claims are allowable, and the application is in condition for allowance. Reconsideration and allowance are respectfully requested. Should any other matters

require attention prior to allowance, it is requested that the Examiner contact the undersigned.

The Commissioner is hereby authorized to charge any fees which may be due for any reason in connection with this communication to Deposit Account No. 23-1703.

Dated: September 13, 2004

Respectfully submitted,



Richard J. Sterner
Reg. No. 35,372
Applicants' Agent

Customer No. 007470
(212) 819-8200

Agent's Direct Line:
(212) 819-8783